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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Mid-Atlantic Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (201) 331-2909

November 26, 1997

WARNING LETTER

Mr. Richard F. Moldin
President & CEO
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, New Jersey 07207

File No.: 98-NWJ-07

Dear Mr. Moldin:

During an inspection of your manufacturing facility located at 200 Elmora Avenue, Elizabeth, New Jersey from August 11 through October 21, 1997, Investigators from this office and Chemists from the New York District Office, documented deviations from Current Good Manufacturing Practice Regulations (cGMPs), Title 21 of the Code of Federal Regulations (CFR), Parts 210 & 211. These observations were noted on the Form FDA483, List of Inspectional Observations, issued to you at the close of the inspection.

The above stated inspection revealed that drug products manufactured at your facility are considered to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act), in that the methods used in, or the facilities and/or controls used in manufacturing are not in conformance with cGMPs, as follows:

Laboratory Issues

1) Laboratory investigations and retests were incomplete in determining assignable cause and/or lacked documentation to invalidate initial out of specification test results, for example:

- Diclofenac Sodium, 50 mg tablets, Lot E129M5V, was retested due to a high blend uniformity result. The sample retest yielded an out of specification result. Resampling at 12 locations yielded in specification results. Initial results were attributed to sampling and analyst errors, without supporting documentation. This lot was used in support of validation for this product.

RELEASE

REVIEWED BY [signature] 12/4/97
C.O. DATE

- Metoprolol Tartrate, 100 mg tablets, Lot 059A6 initially failed core assay. Reinjection of both the original and refiltered solutions confirmed the failing result. Three retests by two different analysts were conducted, however only data obtained by the third analyst was reported and the lot was subsequently released. Documentation was inconclusive to invalidate the initially failing results.

2) There is no assurance that recirculated HPLC solvents have the purity, potency and strength as reported. Although this practice is limited to continuous runs of the same product, there is no data to support the suitability of these recirculated solvents, or the accuracy of data obtained from products analyzed using this method. In addition, there is no written procedure that defines when this practice is implemented.

3) There are insufficient controls in place to ensure the integrity of calculated data generated by the [redacted] software in the Quality Control Laboratory, in that:

- There is no audit trail to track the number of templates accessed to generate data calculations.

- Password protection can be bypassed in the system.

- Data files are automatically deleted after a hardcopy is generated. There is no requirement to identify the analyst or time/date stamping of spreadsheet hardcopies.

4) USP requirements were not met for USP and in-house standards, in that these standards are requalified annually, rather than at time of use, for example:

- USP requires Oxazepam standard be dried at 105° C for 3 hours at 5mm Hg, prior to use.

- USP requires a titrametric water determination be performed on the Propoxyphene Napsylate and Morphine Sulfate standards prior to use.

5) Alternate methods were used in the requalification of working standards without demonstrating equivalence to current USP methods, for example:

- A USP impurity method was used to assay Quinine Sulfate

- In house HPLC methods were used to assay Oxazepam and Clonidine Hydrochloride, instead of the methods identified in the USP 23.

Manufacturing Issues

6) There is no assurance that corrective actions, such as reprocessing and/or visual inspection of finished products, were capable of removing all identified contaminants, for example:

- The blend for Flurazepam 15 mg capsules, Lot E050D7 was found to contain brownish-grey flakes, identified as caramelized lactose, occurring from friction caused in mixing. A screening step was implemented for the blend which further reduced the size of the contaminant. The flakes were then manually removed based on visual inspection and the lot was released.

- One tablet of Propoxyphene Napsylate and APAP 100mg/650mg, Lot 333B7 was found to contain a piece of latex glove. It was unknown at what point the portion of glove was introduced into this batch and total amount of contaminant was unknown. This lot was visually inspected and released.

In addition, the purified water used in Sublot VI of Pentoxyfylline ER Tablets, Lot 546D7, failed Total Organic Carbon due to [redacted] being introduced into the system. Although this sublot was placed on QA hold, it was inadvertently blended with other sublots to make the finished product and was released.

7) The Product Discrepancy Notice (PDN) system was not adequate to ensure complete documentation of discrepancies, investigations and quality unit review for deviations that occurred during manufacturing, for example:

- PDN #97-104 for Carbamazepine 200 mg tablets, Lot 077A7, identified soft, low weight tablets. A partial lot inspection found another soft/low weight tablet and the PDN stated that the entire batch would be visually belt inspected. However, there is no documentation to support that this inspection took place, nor is there any indication of whether similar tablet defects were found. No probable or assignable cause was determined.

- PDN # 97-215 for Oxazepam 10 mg capsules, Lots 710E7, 711E7 & 712E7, identified failing weight variation results due to equipment malfunctions. The outcome determined that all batches be vericapped as a routine process step. Partial lot rejections occurred based on the vericap inspection. The report did not extend review of previously manufactured batches, based on this known equipment problem.

8) Complete equipment qualification was not conducted for the following equipment routinely used in manufacturing:

- [redacted] used for tray drying granulations
- [redacted] fluid bed dryer
- [redacted] Encapsulators

Equipment malfunctions, citing the above units, were described in numerous Product Discrepancy Notices.

Validation Issues

9) Manufacturing process validation was found to be inadequate for the following products, in that portions of batches were rejected that did not meet predetermined specifications:

- 10 out of [redacted] batches of Propoxyphene Napsylate and Acetaminophen 100mg/650mg tablets experienced core tablet sticking throughout compression. Portions of these ten lots were rejected that did not meet specifications.

- Partial lot rejections due to tablet sticking occurred in [redacted] batches of 50 mg strength and [redacted] batches of 100 mg strength Metoprolol Tartrate tablets.

10) Methods used in the stability testing of Oxazepam 10 mg and 15 mg tablets have not been demonstrated to be stability indicating and/or have not been validated. Also, an additional mixing time, after product drying and milling was not included in process validation studies for this product.

11) Deficiencies were noted with validation batches of several products lines:

- Lorazepam 1.0 mg tablets - only 40 samples were tested for content uniformity, this was not representative of the [redacted] tablet batch size. In addition, samples taken of the finished blend exceeded three times the unit dosage weight.

- Acetaminophen and Codeine Phosphate 300mg/30mg & 300mg/60mg tablets - Validation batches E050C6V, E041C6V and 041F8, did not meet in-house specifications for Codeine Phosphate. Also, the validation studies did not support the maximum compression speed specification for this product.

Annual Reports

12) Review of the Annual product report for Acetaminophen & Codeine Phosphate tablets, 300mg/60mg found that information was excluded concerning lots made in 1995, in which several batches exceeded the upper limit for hardness specifications.

13) Several product lines were found to exceed the one year review period, for example:

- Lorazepam 0.5mg, 1.0 mg and 2.0 mg tablets, review covered production from 1/1/95 to 2/28/97
- Diclofenac Sodium 50 mg and 75 md Extended Release tablets, review covered production from 1/1/95 to 12/31/97
- Acetaminophen and Codeine Phosphate 300mg/60mg & 300mg/30mg tablets, review covered production from 1/1/95 to 3/31/97

The above list is not intended to be all-inclusive of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deficiencies. Failure to implement corrective measures may result in regulatory action, including seizure and/or injunction, without further notice.

We are in receipt of your written response, dated November 4, 1997, to the FDA483 List of Inspectional Observations. Comments concerning FDA483 Observations #17 through 20, are limited to a product covered under the pre-approval inspection program and will be responded to under separate cover. We offer the following comments to the remaining responses as they correspond to the FDA483 Observations:

Item 1) The implementation of a decision flow chart, expanding investigations outside the laboratory, increased oversight by QA and re-training Supervisors and Analysts, should assist your firm in conducting more thorough investigations in the future. Documentation should demonstrate confidence in the data represented and the rationale for decisions made to invalidate data, resample and retest. Your corrective actions will be reviewed during the next inspection.

Item 2) Your response appears adequate. We consider product reprocessing the same as product rework, which should be adequately validated if implemented in the future.

Item 3) We note that the practice of recycling of mobile phase has been discontinued and will be authorized only with a validated procedure. The effect of a slight baseline rise as it relates to concurrently increasing the limit of detection and limit of quantitation, should be considered in future validation studies to support this practice.

Item 4) Your procedure appears adequate to address this point and will be evaluated during the next inspection.

Item 5) Your commitment to complete all equipment qualifications by April 1998 is acknowledged. However, it should be noted that using passing finished product test results does not justify the use of unqualified equipment.

Item 6) Your response refers to corrections planned to increase data security, limit access and create a system to identify time, date and analyst. These system corrections will be evaluated during the next inspection.

Item 7) Your response appears adequate.

Item 8) Even though core tablet sticking during compression is considered to be an aesthetic defect, it resulted in portions of ten lots being rejected, which may be indicative of an unvalidated process. This product will be reviewed again during the next inspection.

Item 9) We note your revised SOP which requires working standards to be dried as specified in the USP.

Item 10) Your response refers to FDA's Guide to Inspections of Validation of Cleaning Processes, which states..."The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level, i.e. 50% recovery, 90%, etc." This statement should not be interpreted that 50% recovery is an acceptable level. Your future protocols should establish "acceptable" residue levels, on a product specific basis.

Items 11-13 & 15) Your responses appear adequate and may be subject to review during reinspection.

Item 14) Your response compares data to draw the conclusion that alternate methods are equivalent to USP methods. Your firm needs to demonstrate this by conducting concurrent studies to validate the use of alternate methods.

Item 16) Your response does not address the lower and upper limits of the primary (liquid) and secondary (solid) standards used to

calibrate the [redacted]titration instrument.

Item 21) Your response appears adequate, however it does not address how the Quality Unit review can be improved to prevent recurrence.

Item 22) The retrospective review in support of validating this method, did not include stressed conditions such as fixed high humidity and temperature (75%RH, 40° C).

Items 23-25) Your responses appear adequate and may be subject to review during the next inspection.

Item 26) Your response does not reference what the concentration of the impurity compound and active ingredients are. You should ensure that off-scale peaks are not used to calculate resolution. This observation cited a problem with your review process in assuring correct data is submitted in support of ANDA approval. Efforts should be concentrated in this area to prevent recurrence of this situation.

Item 27) Your response appears adequate, but does not address what steps will be implemented in the future to prevent a similar occurrence.

You should notify this office in writing, within 15 working days of receipt of this letter, of the additional steps you have taken to correct the noted deficiencies. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe within which corrections will be completed.

Your response indicated a desire to meet with District Personnel to offer further explanation of your corrective actions and compliance status. Your additional reply and/or meeting request should be sent to the New Jersey District Office, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Mercedes B. Mota, Compliance Officer.

Sincerely,

Douglas Ellsworth

DOUGLAS ELLSWORTH
District Director
New Jersey District

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

MBM:np